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(54) Method for making uniformly sized particles from water-insoluble organic compounds.

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H. Sonntag, "Lehrbuch der Kolloidwis-
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Description

Background of the invention

5 Particles of compounds having low water-solubility are commonly used in a wide variety of applications, including ceramics, paints, inks, dyes, lubricants, pesticides, insecticides, fungicides, fertilizers, chromatography columns, cosmetics, lotions, ointments, and detergents. Aqueous dispersions of particles are used in many cases to avoid hazards such as a flammability and toxicity associated with organic solvents. Such dispersions typically have a broad range of particle size.

10 In many cases product performance is improved by controlling the particle size distribution. In general, smaller particles of a compound will dissolve faster than larger particles of the same compounds. Control of particle size is, therefore, important in controlling the rate of solubilization.

15 Many drugs have been formulated as particles for controlled-release following oral administration or, implantation. Particle size is one important factor affecting the release rate of these drugs. Those skilled in the art can discern other examples for using particle size to control product performance for the substances listed above.

20 Drugs that are insoluble in water can have significant benefits when formulated as a stable suspension of particles of less than three microns diameter. In this particulate form, the drug can be injected intravenously, circulate in blood, and be preferentially accumulated in, for example, the reticuloendothelial system, where it can facilitate normal reticuloendothelial functions such as detoxification. Alternatively, the drug can reside in the reticuloendothelial cells where it is stored until solubilized or metabolized into an active form which circulates in blood to other tissues for efficacy. This "slow" release of active drug can provide more constant drug concentrations in plasma over a period of hours, days, weeks, or months, resulting in improved therapeutic efficacy. Biodegradable particles which are radiopaque or labelled with a radioisotope are useful for diagnostic

25 imaging of organs, such as liver and spleen, with high concentrations of fixed reticuloendothelial function. Many advantages have already been recognized for insoluble particulate radiopaque contrast media, for example, as explained in "Improvement in Radiographic Contrast Media Through the Development of Colloidal or Particulate Media: an Analysis", by Harry W. Fischer, *Journal of Theoretical Biology*, 67: 653-670 (1977). More recent papers on this subject include Violante, M. R., Fischer, H. W., and Mahoney, J. A., "Particulate Contrast Media", *Invest. Radiol.*, 15: S329 November-December 1980; and Violante, M. R., Dean, P. B., Fischer, H. W., and Mahoney, J. A., "Particulate Contrast Media for Computer Tomographic Scanning of the Liver", *Invest. Radiol.*, 15: 171 November-December 1980.

30 The US-A-3979520 describes a process, wherein rapidly resorbable particulate glibenclamide having a particle surface area of active material of at least 3 m²/g is produced from its solution in an organic solvent by adding the organic solution to an aqueous precipitating solution.

35 There are enormous medical implications for the intravenous administration of drugs formulated as suspensions of particles of three microns diameter, or less, which can be accumulated by phagocytic cells and slowly solubilized for sustained release into plasma for circulation to other organs and tissues. Obvious drug classes appropriate for formulation as particulate suspensions include: antineoplastics, antimicrobials, antivirals, anticoagulants, antihypertensives, antihistamines, antimalarials, male and female contraceptives, antiepileptics, depressants and antidepressants, adrenocortical steroids, hormones and hormone antagonists, cardiac glycosides, immunosuppressants, beta-blockers, water-insoluble vitamins, sympathomimetics, hypoglycemic agents, hyperglycemic agents, analgesics, tranquilizers, mood altering drugs, and others. The treatment of deficiency diseases, alcohol abuse drug abuse, and many others could be improved with intravenous administration of particulate suspensions of the appropriate drug. Other medical applications for particulate drug

45 suspensions will be apparent to those skilled in the art. Accurate control of particle size is essential for safe and efficacious use of these formulations. Particles must be less than three microns in diameter to safely pass through capillaries without causing emboli. This is critical for intravenous administration since the particles must pass through lung capillaries before reaching the fixed reticuloendothelial cells of liver and spleen. Restriction to particle diameters of 0.01-0.1 micron (μm) could result in selective accumulation of these particles in certain tissues, e.g., neoplastic tissue, where capillaries are somewhat more porous than capillaries of normal tissues. Suspensions of particles with diameters greater than 10 microns could be useful for selective intra-arterial administration to purposely embolize vessels feeding abnormal tissue such as a neoplasm. Accurate and precise control of particle diameters is essential

50 for efficacy while minimizing or avoiding adverse effects in each of these applications. Conventional methods of making water-insoluble compound produce particles of many different sizes, many of which are unsuitable for the purpose at hand. Mechanically sorting or separating a desired particle size from a mix of sizes is difficult and unsatisfactory. Centrifuging and filtration do not produce high yields of

particles that are all precisely the same desired size.

Investigations of water-insoluble radiopaque contrast materials required uniform particles in specific sizes that were very difficult to obtain by conventional methods. Precipitation as a way of directly forming particles of a predetermined size was then investigated. Partial success was achieved with one material and one method as reported in "Particulate Contrast Media", *Investigative Radiology*, 15: S329 November-December 1980; but this method would not work with other materials and would not allow accurate variation and control of the particle size produced.

Further investigation led to the invention of this application, which is effective with any drug or other compound having a solubility in water of preferably less than one part per ten thousand to obtain a predetermined particle size of the water-insoluble drugs or other compounds used in aqueous dispersions.

Summary of the invention

The invention involves a method of making uniformly sized particles of a solid, water-insoluble organic compound by, first, preparing a solution of the solid organic compound in a water-miscible organic solvent for the compound, the compound having essentially little aqueous solubility; second, infusing an aqueous precipitating liquid into the solution at a temperature between -10°C and 100°C and at an infusion rate of from 0.01 ml per minute to 1000 ml per minute per unit volume of 50 ml to produce a suspension of precipitated solid organic compound in the form of substantially non-aggregated particles with a substantially uniform mean particle diameter selected from the range of less than 10 microns (μm), wherein the particle size is adjusted by controlling the solution temperature and infusion rate the particle size being directly related to the solution temperature and inversely related to infusion rate, and then separating the particles from the organic liquids and washing in aqueous washing liquid. Agitation of the solution being infused with precipitating liquid is preferred. This can be accomplished by stirring, shaking, combining two streams of liquid, by the infusing itself and by other techniques known to those skilled in the art.

In preferred embodiments of the invention, additional aqueous precipitating liquid is added to the suspension before the particles are separated from the organic solvents. Separation can be accomplished, for example, by centrifugation, membrane filtration, reverse osmosis, or other methods.

The aqueous washing liquid can be the same as the aqueous precipitating liquid, and it can be pharmaceutically acceptable for injecting into a patient.

The aqueous precipitating liquid can be water, a solution of a mineral salt, or a surfactant solution. Suitable aqueous surfactant solutions include 5% polyvinyl pyrrolidone C-30, 0.1% polyvinyl pyrrolidone C-15, 0.1% human serum albumin, 0.1% Pluronic F-68 (poloxamer 188), and 0.33% gelatin, alone or combined with 0.6% hetastarch, 0.02% propylene glycol, or 2% sucrose. The aqueous precipitating liquid can be infused through a needle of standard gauge.

The mean particle diameter of the particles can be up to 10 microns (μm), preferably in a range of 0.01 microns to 5 microns (μm).

Particles made according to this invention will typically have a particle size distribution with a maximum relative standard deviation of 50%, for example 95% of the particle having a mean size of 1.0 micron (μm) will be within the size range of 0.5 to 1.5 microns (μm).

The solid organic compound has, preferably, an aqueous solubility of less than about one part per ten thousand, and the compound may be organo-metallic. Generally, any compound that meets the other requirements of the invention is suitable, including many drugs. Where heparin complexes are used, no surfactant is necessary.

The organic solvent can be dimethyl sulfoxide, dimethyl formamide, N,N'-dimethyl acetamide, phenol, isopropanol, or other solvents.

In a preferred embodiment, the method includes the additional step of diluting the organic solution with a non-solvent liquid such that the ratio of non-solvent to solvent is between 100:1 and 1:100, after preparing the organic solution and before the infusion step, so that the particle size is directly related to the ratio of non-solvent to solvent.

In further preferred embodiments, the non-solvent is one in which the organic compound is slightly more soluble than in water. The non-solvent can be a lower aliphatic alcohol.

In particular preferred embodiments, iodipamide ethyl ester, an ethyl ester of a triiodobenzoic acid derivative, is dissolved in dimethyl sulfoxide and diluted with ethanol; if the ratio of ethanol to dimethyl sulfoxide is greater than about two, the mean particle diameter is greater than about one micron (μm), and if the ratio of ethanol to dimethyl sulfoxide is less than about two, the mean particle diameter is less than about one micron.

Brief description of the drawings

- Figure 1 is a graph of free energy of the various phases of the compounds used in the invention.
- 5 Figure 2 is a graph of the relationship between size distribution of particles and time interval between onset and completion of precipitation.
- Figure 3 is a graph of infusion rate (ml/min.) (of aqueous precipitating liquid) as a function of the product of stir rate (rpm) and total volume (liters) of the organic solution at a constant temperature; the relationship: aqueous infusion rate (ml/min.) = $23 + 0.14$ [stir rate (rpm) x volume organic solution (l)] defines the parameters for production of iodipamide ethyl ester particles of one micron (μ m) diameter at a constant temperature (4°C) and in dimethyl sulfoxide/ethanol;
- 10 Figure 4 is a graph showing iodipamide ethyl ester particle size as a function of temperature at a constant ratio of infusion rate of aqueous precipitating liquid to [stir rate (rpm) x volume of organic solution];
- Figure 5 is a graph demonstrating the effect on particle size of varying the infusion rate of aqueous precipitating liquid at constant temperature and stirring rate of an iodipamide ethyl ester solution; and
- 15 Figure 6 is a schematic diagram of preferred steps in the invention method.

Detailed description of the invention

- 20 This invention concerns the preparation of water-insoluble compounds as uniform particles of a predetermined size. The particles are formed by a carefully controlled precipitation of the compound into an aqueous phase from an organic solvent in which the compound is soluble.

- The physical chemical principles thought to be involved in this invention are demonstrated in figures 1 and 2. Figure 1 shows that the free energy of the system is higher when the compound is dissolved in the organic solvent than when the compound exists in the particulate or crystalline state. During precipitation the compound will naturally convert to the crystalline form-the lowest free energy state-unless it is trapped in the metastable particulate form, a condition where its free energy is intermediate between the solution and the crystalline phases. When properly practiced, this invention enables the trapping of a compound in the metastable particle state, precluding transformation to the crystalline state.
- 25

- 30 The size distribution of particles formed during precipitation can be correlated with the time interval between onset and completion of precipitation. As shown in Figure 2, a very short time interval results in the production of uniformly sized particles (A), while a very long time interval results in a broad particle size distribution (B). Intermediate conditions produce intermediate particle size distributions.

- An important parameter for utilization of this invention is the aqueous solubility of the compound. The invention requires the use of solid organic compounds having essentially little aqueous solubility. We have found that compounds which have a water-solubility of less than one part in ten thousand are ideally suited for this technology. Compounds which are more water-soluble can be used with this invention; however, the higher the solubility the greater the probability that some of the compound will dissolve in the aqueous phase and transform to the more stable crystalline state. Also redissolution in the aqueous phase can lead to a broadening of the particle size distribution. For these reasons, we prefer compounds having a water-solubility of less than one part in ten thousand.
- 35

- In order to make particles of a uniform and predetermined size having a solubility of less than one part per ten thousand, a solution of the solid organic compound in a suitable organic solvent is prepared. The solution may be diluted with a non-solvent that does not cause the drug or other compound to precipitate. An aqueous precipitating liquid is also prepared, preferably with a surfactant, in sufficient quantity to both precipitate the drug or other compound and stabilize the resulting suspension of particles of the compound against aggregation. Water may be used alone as the precipitating liquid when compounds which do not aggregate are used. The aqueous solution is infused into the organic solution under carefully controlled conditions, including: the rate of stirring of the organic solution, the rate of infusion of the aqueous solution, the volume of the organic solution and the temperature of the solutions and the suspension.
- 40

- In investigations of varying parameters to adjust for particle size, three usable relationships were discovered: (1) diluting the solution with more of the non-solvent produces larger particles, and diluting with less of the non-solvent produces smaller particles; (2) higher temperatures of the solution during precipitation produce larger particles, and lower temperatures of the solution during precipitation produce smaller particles; and (3) at a given stirring rate of the organic solution, faster infusion rates of aqueous solution produce smaller particles while slower infusion rates produce larger particles.
- 45

When the precipitation is complete, the uniformly sized particles are separated from the liquid and washed to remove the organic solvent. In most cases, the particles should be separated from the liquid quickly to prevent transformation to a crystalline form.

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Compounds that are used in the invention are solid organic materials, including organometallic compounds, that have a solubility in water of preferably less than one part per ten thousand. Otherwise the specific compound and its purpose are less important to the way the invention works.

5 The first step is to prepare a solution of the compound of interest in an organic solvent suitable for that compound. This can occur as the compound is synthesized as a dissolved solid, or it can be done by simply dissolving the compound in the solvent of choice.

The solvent is chosen to suit the compound. For example, dimethylformamide (DMF) is a solvent for iotalamate ethyl ester (IEE) and iosefamate ethyl ester (IFE), and dimethylsulfoxide (DMSO) is a solvent for iodipamide ethyl ester (IDE) and IEE. Any satisfactory solvent for the compound that is miscible with water can be used.

10 The next step is to dilute the solution with a non-solvent that does not cause the compound to precipitate. The non-solvent causes greater dispersion of the dissolved molecules of the compound in the liquid phase. Greater dilution of the solution with non-solvent produces larger particles, and less dilution of the solution with non-solvent produces smaller particles.

15 The non-solvent should not precipitate the compound when it is added to the solution. Non-solvents in which the compound is slightly more soluble than in water are preferred. Lower aliphatic alcohols, such as ethanol, are effective non-solvents for solutions of IDE and IEE in DMSO. For the ethyl esters of triiodobenzoic acid, proportions of non-solvent to solvent at a ratio of 2 or more can produce 1 to 3 micron (μm) sized particles (depending on other parameters); and ratios of less than 2 can produce sub-micron particles, at least as applied to DMSO solutions diluted with ethanol.

20 To precipitate the compound from the solution in a desired particle size, an aqueous solution of a surfactant is prepared in sufficient quantity to effect complete precipitation of the compound and to stabilize the resulting suspension of particles of the compound against aggregation. The surfactant provides the stabilization against aggregation, and the water is the precipitating agent. Presence of extra surfactant is advisable to ensure stabilization so that precipitated particles suspended in liquid do not aggregate, forming particles of an improperly large size. While surfactants are used in most cases, some compounds appear to form stable, substantially non-aggregated particles without the use of surfactants. Examples of such non-aggregating compounds are certain Heparin complexes.

30 It is thought that particles with relatively high surface charge are less likely to require surfactant in the aqueous precipitating solution. The surface charge of a particle is sometimes referred to as its zeta potential, a measurement of charge which falls off with distance. There may be a threshold zeta potential above which no surfactant is needed, but below which, surfactant is needed to keep the precipitating particles from aggregating. The zeta potential is directly correlated with the polarity or net charge of an organic compound. Thus, the need for surfactant in the aqueous precipitating solution may be predicted from the extent of the charge or polarity of the organic compound employed in the method of the invention. For example, heparin complexes are highly charged, and form stable non-aggregated particles when precipitated with water.

35 Generally, such a theory notwithstanding, empirical methods will suffice; that is, a precipitation may first be performed with water, and if aggregation occurs, then a precipitation in the presence of surfactant is indicated. Surfactants are chosen for their compatibility with the compound and their ability to stabilize a suspension of compound particles. For work with IEE and IDE drugs, a solution of 5% polyvinyl pyrrolidone (C-30), 0.1% polyvinyl pyrrolidone (C-15), or 0.1% human serum albumin is preferred. Also 0.1% Pluronic F- 68, [Poloxamer 188, a poly(oxyethylene-co-oxypropylene) polymer], a 0.33% gelatin, 0.33% gelatin plus 0.6% Hetastarch, 0.33% gelatin plus 0.002% propylene glycol, and 0.33% gelatin plus 2% sucrose, or other surfactants known to one skilled in the art can be used.

40 To precipitate compound particles in the desired sizes, the aqueous solution and the organic solution are combined under controlled conditions of temperature, ratio of infusion rate to stirring rate, and the proportion of non-solvent to solvent in the dispersed solution.

50 The precipitation of the compound occurs exothermically, heating the organic solution and the resulting suspension. The temperature of the solution and resulting suspension is controlled to achieve the particle size of precipitate that is desired. Higher solution temperatures during precipitation produce larger particles, and lower solution temperatures during precipitation produce smaller particles.

Also, faster infusion rates at constant stirring rate of organic solution produce smaller particles, and slower infusion rates produce larger particles.

55 Figures three to five show the effects on particle size of varying parameters during precipitation of IDE from a DMSO solution diluted with 1 part solution to 2 parts ethanol using an aqueous solution of 5% polyvinyl pyrrolidone at different infusion rates and temperatures.

Fig. 3 shows that as the volume and stirring rate of the organic compound iodipamide ethyl ester and dimethyl sulfoxide/ethanol solution are increased, the infusion rate of aqueous surfactant solution must be in-

creased proportionally as defined by: infusion rate (ml/min.)= $23+0.14$ [volume (liters) \times stir rate (r.p.m)] to produce particles of 1 micron diameter at 4°C.

Fig. 4 shows that at a constant ratio of infusion rate to [stir rate \times volume], increased precipitation temperature produces larger particles.

Fig. 5 plots 3 points from the 20°C temperature line of Fig. 3 for rate of infusion of the precipitation liquid into the organic solution to approximate the curve by which larger particles are formed from slower injection rates, showing that at a constant ratio of temperature to [stir rate \times volume], particle size is inversely related to the rate of infusion of the precipitating liquid.

When Figs. 3-5 are considered together, they show clearly that higher temperatures and slower mixing rates produce larger particles, the lower temperatures and faster mixing rates produce smaller particles. Another parameter that can be varied to affect particle size is the amount of dilution of the solution before precipitation occurs.

When the precipitation is complete, extra aqueous surfactant solution can be added to further stabilize the suspended particles against agglomeration. The extra solution can be added at a rapid rate, since essentially all the compound is now precipitated in uniformly sized particles. The precipitated particles are promptly separated from the organic solvents to prevent redissolving and reprecipitation of particles at undesirable sizes. Centrifuging is a preferred way to perform the separation. Other methods, including membrane filtration, reverse osmosis, and others known to persons skilled in the art may also be used to remove undesired substances. Promptly after separating the particles from the organic liquid, the particles are washed or rinsed with normal saline solution to remove solvent and excess surfactant.

The method of the invention is illustrated by the following examples which, however, do not limit the invention as described above and set forth in the Claims.

Examples 1 to 19 are presented in Table I. The solid organic compound was dissolved in the organic solvent and then diluted (except where indicated) by the non-solvent. The aqueous precipitating liquid was then infused through a needle at the given rate into the solution, at the given temperature and while stirring at the given stirring rate. The size of the particles obtained is shown for example example.

TABLE Ia

	Example 1	Example 2
1. Solid organic compound	10 mg 2,2',4,4',-tetrahydroxybenzophenone	1.4 mg RS nitro-cellulose compound (1/4 sec)
2. Organic solvent	0.2 ml dimethyl sulfoxide	0.2 ml dimethyl sulfoxide
3. Non-solvent	0.2 ml ethanol (99%)	0.2 ml ethanol (99%)
4. Aqueous precipitating liquid	5 ml human serum albumin (0.1%)	5 ml human serum albumin (0.1%)
5. Infusion rate (ml/min.) of precipitation liquid	2.5	2
6. Stir rate (rev./min) of solution	200	400
7. Temperature of solution	20°C	20°C
8. Particle diameter (μ m)	0.5 micron	0.5 micron

TABLE Ib

		Example 3	Example 4
5	1. Solid organic compound	7 mg RS nitrocellulose (1/4 sec.)	10 mg progesterone
10	2. Organic solvent	0.4 ml dimethyl sulfoxide	0.2 ml dimethyl sulfoxide
	3. Non-solvent	0.01 ml isopropanol	0.1 ml ethanol (99%)
15	4. Aqueous precipitating liquid	5 ml human serum albumin (0.1%)	5 ml human serum albumin (0.1%)
	5. Infusion rate (ml/min.) of precipitating liquid	2.5	2.5 (through an 18 gauge needle)
20	6. Stir rate (rev./min) of solution	200	200
	7. Temperature of solution	20°C	20°C
25	8. Particle diameter (μm)	0.5 micron	1 micron

TABLE Ic

		Example 5	Example 6
35	1. Solid organic compound	5240 mg iosefamate ethyl ester	10 g iothalamate ethyl ester
	2. Organic solvent	60 ml dimethyl sulfoxide	32 ml dimethyl sulfoxide
40	3. Non-solvent	20 ml ethanol (99%)	—
	4. Aqueous precipitating liquid	400 ml polyvinyl pyrrolidone C-15 (5%)	800 ml polyvinyl pyrrolidone C-15 (5%)
45	5. Infusion rate (ml/min.) of precipitating liquid	3	300
	6. Stir rate (rev./min) of solution	200	300
50	7. Temperature of solution	20°C	0—2°C initial 40°C final
55	8. Particle diameter (μm)	1.0 micron	1.0 micron

TABLE Id

		Example 7	Example 8
5	1. Solid organic compound	100 mg beta-2,3,6 triod-3-dimethyl formamidino-phenyl propionic acid ethyl ester	100 mg beta-2,3,6 triod-3-dimethyl formamidino-phenyl propionic acid ethyl ester
10	2. Organic solvent	2.0 ml dimethyl sulfoxide	2.0 ml dimethyl sulfoxide
15	3. Non-solvent	2.5 ml ethanol (99%)	2.5 ml ethanol (99%)
	4. Aqueous precipitating liquid	25 ml Poloxamer 188 a poly (oxyethylene-co-oxypropylene) polymer (Pluronic F-68)(0.1%)	25 ml human serum albumin (0.1%)
20	5. Infusion rate (ml/min.) of precipitating liquid	750	750
25	6. Stir rate (rev./min) of solution	650	650
	7. Temperature of solution	10°C	10°C
30	8. Particle diameter (μm)	0.1 micron	0.1 micron

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TABLE Ie

		Example 9	Example 10
5			
	1. Solid organic compound	100 mg beta 2,4,6-triiod-3-dimethyl formamidino phenyl propionic acid ethyl ester	120 mg iodipamide ethyl ester
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	2. Organic solvent	2.0 ml dimethyl sulfoxide	2.0 ml dimethyl sulfoxide
15	3. Non-solvent	2.5 ml ethanol (99%)	2.5 ml ethanol (99%)
	4. Aqueous precipitating liquid	25 ml polyvinyl pyrrolidone C-15 (0.1%)	5 ml polyvinyl pyrrolidone C-15 (0.1%)
20			
	5. Infusion rate (ml/min.) of precipitating liquid	750	300
	6. Stir rate (rev./min) of solution	650	80
25			
	7. Temperature of solution	10°C	4°C
	8. Particle diameter (µm)	0.1 micron	0.1 micron
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TABLE If

		Example 11	Example 12	
5	1.	Solid organic compound	1200 mg iodipamide ethyl ester	120 mg iodipamide ethyl ester
10	2.	Organic solvent	20 ml dimethyl sulfoxide	2.0 ml dimethyl sulfoxide
	3.	Non-solvent	25 ml ethanol (99%)	2.5 ml ethanol (99%)
15	4.	Aqueous precipitating liquid	50 ml polyvinyl pyrrolidone C-15 (0.1%)	5.0 ml polyvinyl pyrrolidone C-15 (0.1%)
	5.	Infusion rate (ml/min) of precipitating liquid	19	2
20	6.	Stir rate (rev./min) of solution	190	200
	7.	Temperature of solution	10°C	10°C
25	8.	Particle diameter (μm)	1.5 micron	1.0 micron

TABLE Ig
Example 13

Example 14

35	1.	Solid organic compound	120 mg iodipamide ethyl ester	10 mg isopropyl pyrrolizine derivative (NSC-278214)
	2.	Organic solvent	2.0 ml dimethyl sulfoxide	0.4 ml dimethyl sulfoxide
40	3.	Non-solvent	2.5 ml ethanol (99%)	—
45	4.	Aqueous precipitating liquid	25 ml poly(oxyethylene co-oxypropylene) polymer, Poloxamer 188 (Pluronic F-65) (0.1%)	5 ml human serum albumin (0.1%)
	5.	Infusion rate (ml/min.) of precipitating liquid	750	20
50	6.	Stir rate (rev./min) of solution	700	300
	7.	Temperature of solution	0°C	17°C
55	8.	Particle diameter (μm)	0.1 micron	0.5 micron

TABLE Ia
Example 15

Example 16

1.	Solid organic compound	10 mg isopropyl pyrrolizine derivative (NSC-278214)	10 mg isopropyl pyrrolizine derivative (NSC-278214)
2.	Organic solvent	0.4 ml N,N'-dimethyl acetamide	0.4 ml dimethyl sulfoxide
3.	Non-solvent	—	0.2 ml ethanol (99%)
4.	Aqueous precipitating liquid	20 ml human serum albumin (0.1%)	20 ml human serum albumin (0.1%)
5.	Infusion rate (ml/min.) of precipitating liquid	38	100
6.	Stir rate (rev./min) of solution	50	200
7.	Temperature of solution	0°C	0°C
8.	Particle diameter (μm)	0.5 micron	0.1 micron

TABLE II

		Example 17	Example 18
5	1. Solid organic compound	1.5 mg. 1,2 diamino-cyclohexane malinate platinum (II)	10 mg N-(trifluoroacetyl) adriamycin 14 valerate
10	2. Organic solvent	0.05 ml phenol	0.2 ml dimethyl sulfoxide
	3. Non-solvent	0.45 ml m-amino-phenol and 0.25 ml ethanol (99%)	0.2 ml ethanol (99%)
15	4. Aqueous precipitating liquid	5 ml human serum albumin (0.1%)	5 ml human serum albumin (0.1%)
20	5. Infusion rate (ml/min.) of precipitating liquid	5	2.5
	6. Stir rate (rev./min) of solution	200	200
25	7. Temperature of solution	20°C	20°C
	8. Particle diameter (μm)	0.1 micron	1.0 micron

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TABLE Ij

		Example 19	Example 20
5			
10	1. Solid organic compound	200 mg heparin-benzalkonium chloride complex	10 mg organic compound* (see list)
	2. Organic solvent	10 ml isopropanol	0.2 ml dimethyl sulfoxide
15	3. Non-solvent	—	0.2 ml ethanol (99%)
	4. Aqueous precipitating liquid	200 ml water	5 ml human serum albumin (0.1%)
20	5. Infusion rate (ml/min.) of precipitating liquid	3.7	2.5
	6. Stir rate (rev./min) of solution	300	250
25	7. Temperature of solution	20°C	20°C
	8. Particle diameter (μm)	0.5 micron	1.0 micron

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*norethisterone,
acetyl salicylic acid,
wafarin,
heparin-tridodecyl methyl ammonium chloride complex,
sulfamethoxazole,
cephalexin,
prednisolone acetate,
diazepam,
clonazepam,
methidone,
naloxone,
disulfiram,
mercaptopurine,
digitoxin,
primaquine,
mefloquine,
atropine,
scopolamine,
thiazide,
furosemide,
propranolol,
methyl methacrylate,
poly methyl methacrylate,
5-fluorodeoxyuridine,
cytosine arabinoside,
acyclovir,
levonorgestrel

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Examples 1 to 19 show how the process can be used to produce aqueous dispersions of a wide variety of compounds that have low aqueous solubility for which particle size can be controlled with substantial precision and predictability. Conditions would be varied from compound to compound according to the invention in order to optimize results. This may in some cases include chemical modification of the compound to achieve

the desired solubility.

Because of the range of examples presented above, it is reasonable to one skilled in the art, that numerous other compounds would be expected to behave in similar fashion.

5 Example 20 is also presented in Table I. This example should be preferred in the same manner as examples 1 to 19, and would make particles of the listed compounds within the scope of the invention.

10 Examples 21 to 28 are presented in Table II. In each example, the given quantity of iodipamide ethyl ester was dissolved in the given volume of dimethyl sulfoxide, then diluted with the given volume of ethanol. The aqueous precipitating liquid was prepared from polyvinylpyrrolidone then infused at the given infusion rate through a needle with the given gauge into the solution while the solution was stirred at the given stir rate. The precipitation was carried out in the given vessel at the given temperature. After precipitation, the given amount of saline was added to further stabilize the dispersion. In each example, the mean particle diameter was about 1.0 micron (μm) and substantially uniform.

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TABLE IIa

Parameters for iodipamide ethyl ester particle precipitation

	Example 21	Example 22	Example 23
20 Material	0.5 gm	1 gm	2 gm
Iodipamide ethyl ester (60 mg/ml)	10 ml	20 ml	40 ml
25 Ethanol (99%)	12.5 ml	25 ml	50 ml
Polyvinyl pyrrolidone	25 ml	50 ml	100 ml
0.9% saline	15 ml	30 ml	60 ml
30 Stir rate	125 rpm	190 rpm	300 rpm
Temperature	4°C	4°C	4°C
Infusion rate	11 ml/min	19 ml/min	30 ml/min
35 Infusion needle size	19 g	19 g	19 g
S.B. length	1.5" (3,8 cm)	1.5" (3,8 cm)	1,5" (3,8 cm)
Vessel diam.	2.38" (6,05 cm)	2.38" (6,05 cm)	2.38" (6,05 cm)
40 Vessel	250 ml	250 ml	250 ml
	Polypropylene bottle	polypropylene bottle	polypropylene breaker

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TABLE IIb

Parameters for iodipamide ethyl ester particle precipitation

	Example 24	Example 25	Example 26
Material	3.5 gm	5 gm	10 gm
Iodipamide ethyl ester (60 mg/ml)	70 ml	100 ml	200 ml
Ethanol (99%)	87.5 ml	125 ml	250 ml
Polyvinyl pyrrolidone	175 ml	250 ml	500 ml
0.9% saline	105 ml	150 ml	300 ml
Stir rate	330 rpm	200 rpm	300 rpm
Temperature	—	—	—
Infusion rate	45 ml/min	60 ml/min	85 ml/min
Infusion needle size	19 g	18 g	18 g
S. B. length	1.88" (4.78 cm)	2.75" (6.99 cm)	2.75" (6.99 cm)
Vessel diam.	3.38" (8.59 cm)	5.0" (12.7 cm)	5.0" (12.7 cm)
Vessel	1,000 ml	2,000 ml	2,000 ml
	Glass beaker	Glas beaker	Glass

TABLE IIc

Parameters for iodipamide ethyl ester particle precipitation

	Example 27	Example 28
Material	20 gm	40 gm
Iodipamide ethyl ester (60 mg/ml)	400 ml	800 ml
Ethanol (99%)	500 ml	1,000 ml
Polyvinyl pyrrolidone	1,000 ml	2,000 ml
0.9% saline	600 ml	1,200 ml
Stir rate	175 rpm	210 rpm
Temperature	—	—
Infusion rate	120 ml/min	175 ml/min
Infusion needle size	16 g	16 g
S. B. length	3.25" (8,26 cm)	3.25" (8,26 cm)
Vessel diam.	8.6" (21,8 cm)	8.6" (21,8 cm)
Vessel	9 L	9 L
	Belco vessel	Belco vessel

Example 29

Preparation of iodipamide ethyl ester particles for administration to a patient

Particles of iodipamide ethyl ester (IDE) with a size of above 1 micron may be prepared for administration to a patient. IDE is the water-insoluble ethyl ester of iodipamide, a water-soluble radiopaque compound used clinically for radiographic examination of the gallbladder. The synthesis of iodipamide ethyl ester is known in the art (for example, esterification by alcohol and acid or by a Schotten-Bauman reaction).

IDE is only minimally soluble in water (10^{-5} M) and can be precipitated easily from the dimethyl sulfoxide (DMSO)/ethanol solvent mixture. However, the simple addition of water to this solution results in IDE particles with extremely rough contours; these particles vary in size from less than one micron (μ m) to greater than 300 microns (μ m) in diameter. In light of the problems that rough contours could damage vascular endothelial cells and promote aggregation, and that large particles could create pulmonary emboli, the method of this invention provides a more refined procedure for controlling particle size and shape.

Particle precipitation procedure

Physical methods for modifying and controlling particle size, such as ball milling, grinding or sonication result in preparations with a very broad range of particle diameters. These methods are commonly used to eliminate large particles (greater than 4-5 microns (μ m)) which could embolize in the pulmonary capillary bed, but generally some particles of submicron size are also produced; these very small particles have been shown to be more toxic than 1-2 micron particles, possibly due to increased protein binding resulting from the much larger surface area inherent with particles of smaller diameters, or possibly because of excessive uptake by bone marrow cells.

A chemical precipitation procedure for producing particles of a given size was developed to avoid these problems. By adding an aqueous solution of polyvinyl pyrrolidone, at controlled rates and temperatures, to IDE

dissolved in a dimethyl sulfoxide/ethanol solvent, apparently spherical, amorphous particles can be produced with an extremely narrow size distribution. For a particle preparation with a mean diameter 1 of micron (μm), the total range of particle diameters is 0.4 to 2.0 (μm) microns with 90 per cent of the particles ranging in size
 5 between 0.5 and 1.5 microns (μm) as determined by microscopy.

Claims

- 10 1. A method of making uniformly sized particles of a solid, water-insoluble organic compound, comprising:
 - (a) preparing a solution of the solid organic compound in a water-miscible organic solvent for the compound, the solid organic compound having essentially little aqueous solubility;
 - 15 (b) infusing an aqueous precipitating liquid into the organic solution at a temperature between -10°C and 100°C and at an infusion rate of from 0.01 ml per min. to 1000 ml per min. per 50 ml unit volume of solution, so as to produce a suspension of precipitated solid organic compound in the form of substantially non-aggregated particles of a uniform size selected from a mean particle diameter range of up to 10 microns (μm), wherein the particle size is adjusted by controlling the solution temperature and infusion rate the particle size being directly related to the solution temperature during precipitation and inversely related to the infusion rate;
 - 20 (c) separating the particles from the organic liquids and washing in aqueous washing liquid.
2. The method according to Claim 1, wherein additional aqueous precipitating liquid is added to the suspension before the particles are separated.
- 25 3. The method according to Claim 1, wherein the particles are separated by centrifugation, membrane filtration, or reverse osmosis.
4. The method according to Claim 1, wherein the aqueous washing liquid is the same as the aqueous precipitating liquid.
- 30 5. The method according to Claim 1, wherein the aqueous washing liquid is pharmaceutically acceptable for injection into a patient.
6. The method according to Claim 1, wherein the aqueous precipitating liquid is selected from the group consisting of water and an aqueous solution of a mineral salt.
- 35 7. The method according to claim 1, wherein the aqueous precipitating liquid is a surfactant solution.
8. The method according to Claim 1, wherein the precipitating liquid is a surfactant solution selected from the group consisting of 5% polyvinyl pyrrolidone in water, 0.1% polyvinyl pyrrolidone in water, 0.1% human serum albumin in water, 0.1% Pluronic F-68 in water, 0.33% gelatin in water, 0.33% gelatin and 0.6% he-
 40 tastarch in water, 0.33% gelatin and 0.02% propylene glycol in water, and 0.33% gelatin and 2% sucrose in water.
9. The method according to Claim 1, wherein the aqueous precipitating liquid is infused by means of a needle
 45 of standard gauge.
10. The method according to Claim 1, wherein the mean particle diameter is selected from the range of from 0.01 micron to 0.1 micron (μm).
- 50 11. The method according to Claim 1, wherein the mean particle diameter is selected from the range of from 1 micron to 4 microns (μm).
12. The method according to Claim 1, wherein the mean particle diameter is from 1 to 10 microns (μm).
13. The method according to Claim 1, wherein the solid organic compound has an aqueous solubility of less
 55 than about one part per ten thousand at ambient temperature.
14. The method according to Claim 1, wherein the solid organic compound is an organometallic compound.
15. The method according to Claim 1, wherein the solid organic compound is selected from the group con-

- 5 sisting of an antineoplastic, an antimicrobial, an antiviral, an anticoagulant, an antihypertensive, an anti-histamine, an antimalarial, a contraceptive, an antiepileptic, a depressant, an antidepressant, an adrenocortical steroid, a hormone, a hormone antagonist, a cardiac glycoside, an immunosuppressant, a beta-blocker, a water-insoluble vitamin, a sympathomimetic, a hypoglycemic agent, a hyperglycemic agent, an analgesic, a tranquilizer, and a mood-altering drug.
16. The method according to Claim 1, wherein the solid organic compound is an ethyl ester of a triiodobenzoic acid derivative.
- 10 17. The method according to Claim 1, wherein the solid organic compound is selected from the group consisting of iodipamide ethyl ester, iothalamate ethyl ester, isoeufamate ethyl ester, 2,2',4,4'-tetrahydroxybenzophenone, RS nitrocellulose, progesterone, beta-2,4,6-triiodo-3-dimethyl formamidinophenyl propionic acid ethyl ester, isopropylpyrrolizine derivative (NSC-278214), N-(trifluoroacetyl) Adriamycin 14 valerate, and 1,2 diaminocyclohexane malinate platinum (II).
- 15 18. The method according to Claim 1, wherein the solid organic compound is selected from the group consisting of norethisterone, acetyl salicylic acid, wafarin, heparinridodecyl methyl ammonium chloride complex, sulfamethoxazole, cephalexin, prednisolone acetate, diazepam, clonazepam, methidone, naloxone, disulfiram, mercaptopurine, digitoxin, primaguine, mefloquine, atropine, scopalamine, thiazide, furose-
20 mide, propanelol, methyl methacrylate, poly methyl methacrylate, 5-fluorodeoxyuridine, cytosine arabinoside, acyclovir, levonorgestrel.
19. The method according to Claim 1, wherein the organic solvent is from the group consisting of dimethyl sulfoxide, dimethyl formamide, N,N'-dimethyl acetamide, phenol, and isopropanol.
- 25 20. The method according to Claim 1, wherein the solid organic compound is a heparin complex, the organic solvent is isopropanol, and the aqueous precipitating liquid is water or an aqueous mineral salt solution.
21. The method according to Claim 1, which further comprises the step of diluting the organic solution with a non-solvent liquid such that the ratio of non-solvent to solvent is between 100:1 and 1:100, after the
30 preparation of the solution and before the infusion step, the particle size being directly related to the ratio of non-solvent to solvent.
22. The method according to Claim 21, wherein the non-solvent liquid is one in which the solid organic compound is slightly more soluble than in water.
- 35 23. The method according to Claim 21, wherein the non-solvent liquid is a lower aliphatic alcohol.
24. The method according to Claim 21, wherein the solid organic compound is selected from the group consisting of iodipamide ethyl ester and iosefamate ethyl ester, the organic solvent is dimethyl sulfoxide, the
40 non-solvent liquid is ethanol, the ratio of ethanol to organic solution is greater than 2.0, and the mean particle diameter is greater than 1 micron(μm) in diameter.
25. The method according to Claim 21 wherein the solid organic compound is selected from the group consisting of iodipamide ethyl ester and iosefamate ethyl ester, the organic solvent is dimethyl sulfoxide, the
45 non-solvent liquid is ethanol, the ratio of ethanol to organic solution is less than 2.0, and the mean particle diameter is less than about one micron in diameter.
26. The method according to Claim 21, wherein the solid organic compound is iodipamide ethyl ester, the organic solvent is dimethyl sulfoxide, the non-solvent is ethanol, the aqueous precipitating liquid is 5%
50 polyvinyl pyrrolidone in water, the temperature is 4°C, and the infusion rate (ml/min) equals 23 ± 0.14 [stir rate (r.p.m.)] \times [volume organic solvent (liters)], and the mean particle diameter is about 1 micron diameter.
27. The method according to Claim 1 wherein the mean particle diameter is selected from the range of from 0.01 micron to 10 microns (μm).
- 55 28. The method according to Claim 1, wherein the mean particle diameter is selected from the range of from 0.01 micron to 5 microns (μm).
29. The method according to Claim 1 wherein the particle size distribution has a maximum relative standard

deviation of 50 percent.

- 5 30. The method according to Claim 1 wherein the organic solution is agitated while the precipitating liquid is being infused.

Patentansprüche

- 10 1. Verfahren zur Herstellung von gleichmäßig großen Teilchen einer festen, wasserunlöslichen organischen Verbindung, umfassend:
- (a) Herstellung einer Lösung der festen organischen Verbindung in einem mit Wasser mischbaren organischen Lösungsmittel für die Verbindung, wobei die feste organische Verbindung im wesentlichen geringe Wasserlöslichkeit aufweist;
- 15 (b) Einbringen einer wäßrigen Fällungsflüssigkeit in die organische Lösung bei einer Temperatur zwischen -10°C und 100°C und mit einer Einbringungsgeschwindigkeit von 0,01 ml/Minute bis 1000 ml/Minute pro 50 ml Einheitsvolumen der Lösung, wobei eine Suspension der ausgefällten festen organischen Verbindung in Form von im wesentlichen nicht aggregierten Teilchen einer gleichmäßigen Größe mit einem mittleren Teilchendurchmesserbereich bis zu 10 Mikron (μm) erhalten wird, wobei die Teilchengröße durch Regulierung der Lösungstemperatur und der Zugabegeschwindigkeit angepaßt wird und die Teilchengröße direkt der Temperatur der Lösung während der Fällung und indirekt der Zugabegeschwindigkeit proportional ist;
- 20 (c) Abtrennen der Teilchen aus den organischen Flüssigkeiten und Waschen in wäßriger Waschflüssigkeit.
- 25 2. Verfahren nach Anspruch 1, in dem zusätzliche wäßrige Fällungsflüssigkeit der Suspension zugegeben wird, bevor die Teilchen abgetrennt werden.
3. Verfahren nach Anspruch 1, in dem die Teilchen durch Zentrifugieren, Membranfiltration oder Umkehrosmose abgetrennt werden.
- 30 4. Verfahren nach Anspruch 1, in dem die wäßrige Waschflüssigkeit die gleiche wie die wäßrige Fällungsflüssigkeit ist.
5. Verfahren nach Anspruch 1, in dem die wäßrige Waschflüssigkeit eine zur Injektion in einem Patienten pharmazeutisch verträgliche Flüssigkeit ist.
- 35 6. Verfahren nach Anspruch 1, in dem die wäßrige Fällungsflüssigkeit Wasser oder eine wäßrige Lösung eines Mineralsalzes ist.
- 40 7. Verfahren nach Anspruch 1, in dem die wäßrige Fällungsflüssigkeit eine Netzmittel-Lösung ist.
8. Verfahren nach Anspruch 1, in dem die Fällungsflüssigkeit eine Netzmittellösung aus der Gruppe 5 % Polyvinylpyrrolidon in Wasser, 0,1 % Polyvinylpyrrolidon in Wasser, 0,1 % menschliches Serumalbumin in Wasser, 0,1 % Pluronic F-68 in Wasser, 0,33 % Gelatine in Wasser, 0,33 % Gelatine und 0,6 % Hetastärke in Wasser, 0,33 % Gelatine und 0,02 % Propylenglykol in Wasser und 0,33 % Gelatine und 2 % Saccharose in Wasser ist.
- 45 9. Verfahren nach Anspruch 1, in dem die wäßrige Fällungsflüssigkeit mit Hilfe einer Nadel mit Standard-Kaliber zugegeben wird.
- 50 10. Verfahren nach Anspruch 1, in dem der mittlere Teilchendurchmesser im Bereich von 0,01 bis 0,1 Mikron (μm) liegt.
11. Verfahren nach Anspruch 1, in dem der mittlere Teilchendurchmesser im Bereich von 1 bis 4 Mikron (μm) liegt.
- 55 12. Verfahren nach Anspruch 1, in dem der mittlere Teilchendurchmesser 1 bis 10 Mikron (μm) beträgt.
13. Verfahren nach Anspruch 1, in dem die feste organische Verbindung eine Wasserlöslichkeit von weniger als etwa 1 Teil pro 10 000 Teile bei Raumtemperatur aufweist.

14. Verfahren nach Anspruch 1, in dem die feste organische Verbindung eine organometallische Verbindung ist.
- 5 15. Verfahren nach Anspruch 1, in dem die feste organische Verbindung ausgewählt ist aus der Gruppe der antineoplastischen, antimikrobiellen, antiviralen, antikoagulierenden und blutdrucksenkenden Wirkstoffe, der Antihistaminika, antimalaria, empfängnisverhütenden, antiepileptischen, depressiven und antidepressiven Wirkstoffe, der Nebennierenrindensteroiden, Hormone, Hormon-Antagonisten, Herz-Glykoside, Immunsuppressoren, Beta-Blocker, wasserunlöslichen Vitamine, Sympathomimetika, hypoglykämischen Wirkstoffe, hyperglykämischen Wirkstoffe, Analgetika, Tranquilizer und stimmungsverändernden Arznei-
10 stoffe.
16. Verfahren nach Anspruch 1, in dem die feste organische Verbindung ein Ethylester eines Trijodbenzoesäure-Derivates ist.
- 15 17. Verfahren nach Anspruch 1, in dem die feste organische Verbindung ausgewählt ist aus der Gruppe Jodipamidethylester, Iothalamatethylester, Iosefamatethylester, 2,2',4,4'-Tetrahydroxybenzophenon, RS Nitrocellulose, Progesteron, β -2,4,6-Trijod-3-dimethylformamidinophenyl-propionsäureethylester, Isopropylpyrrolizin-Derivat (NSC-278214), N-(Trifluoracetyl) Adriamycin 14-valerat und 1,2-Diaminocyclohexanmalinat-Platin (II).
20
18. Verfahren nach Anspruch 1, in dem die feste organische Verbindung ausgewählt ist aus der Gruppe Norethisteron, Acetylsalicylsäure, Wafarin, Heparin-tridodecylmethylammoniumchlorid-Komplex, Sulfamethoxazol, Cephalexin, Prednisolonacetat, Diazepam, Clonazepam, Methidon, Naloxon, Disulfiram, Mercaptopurin, Digitoxin, Primaquin, Mefloquin, Atropin, Scopolamin, Thiazid, Furosemid, Propanolol, Methylnmethacrylat, Polymethylnmethacrylat, 5-Fluordeoxyuridin, Cytosinarabinosid, Acyclovir und Levonorgestrel.
25
19. Verfahren nach Anspruch 1, in dem das organische Lösungsmittel aus der Gruppe Dimethylsulfoxid, Dimethylformamid, N,N'-Dimethylacetamid, Phenol und Isopropanol stammt.
30
20. Verfahren nach Anspruch 1, in dem die feste organische Verbindung ein Heparinkomplex, das organische Lösungsmittel Isopropanol und die wäßrige Fällungsflüssigkeit Wasser oder eine wäßrige Mineralsalzlösung ist.
- 35 21. Verfahren nach Anspruch 1, welches nach der Herstellung der Lösung und vor der Zugabestufe zusätzlich die Stufe der Verdünnung der organischen Lösung mit einer nichtlösenden Flüssigkeit umfaßt, so daß das Verhältnis von Nichtlösungsmittel zu Lösungsmittel zwischen 100:1 und 1:100 liegt, wobei die Teilchengröße eine direkte Funktion des Verhältnisses von Nichtlösungsmittel zu Lösungsmittel ist.
- 40 22. Verfahren nach Anspruch 21, in dem die nicht-lösende Flüssigkeit eine solche ist, in der die feste organische Verbindung etwas mehr löslich ist als in Wasser.
23. Verfahren nach Anspruch 21, in dem die nicht-lösende Flüssigkeit ein niedriger aliphatischer Alkohol ist.
- 45 24. Verfahren nach Anspruch 21, in dem die feste organische Verbindung ausgewählt ist aus der Gruppe Iodipamidethylester und Iosefamatethylester, das organische Lösungsmittel Dimethylsulfoxid ist, die nicht-lösende Flüssigkeit Ethanol ist, das Verhältnis von Ethanol zu organischer Lösung größer als 2,0 ist und der mittlere Teilchendurchmesser größer als 1 Mikron (μm) ist.
- 50 25. Verfahren nach Anspruch 21, in dem die feste organische Verbindung ausgewählt ist aus der Gruppe Iodipamidethylester und Iosefamatethylester, das organische Lösungsmittel Dimethylsulfoxid ist, die nicht-lösende Flüssigkeit Ethanol ist, das Verhältnis von Ethanol zu organischer Lösung kleiner als 2,0 ist und der mittlere Teilchendurchmesser kleiner als etwa 1 Mikron ist.
- 55 26. Verfahren nach Anspruch 21, in dem die feste organische Verbindung Iodipamidethylester ist, das organische Lösungsmittel Dimethylsulfoxid ist, das Nichtlösungsmittel Ethanol ist, die wäßrige Fällungsflüssigkeit 5 % Polyvinylpyrrolidon in Wasser ist, die Temperatur 4°C beträgt, die Zugabegeschwindigkeit (ml/Minute) $23 + 0,14 [\text{Rührgeschwindigkeit (U.p.M.)}] \times [\text{Volumen des organischen Lösungsmittels (Liter)}]$ beträgt und der mittlere Teilchendurchmesser etwa 1 Mikron beträgt.

27. Verfahren nach Anspruch 1, in dem der mittlere Teilchendurchmesser im Bereich von 0,01 bis 10 Mikron (μm) liegt.
- 5 28. Verfahren nach Anspruch 1, in dem der mittlere Teilchendurchmesser im Bereich von 0,01 bis 5 Mikron (μm) liegt.
29. Verfahren nach Anspruch 1, in dem die Teilchengrößenverteilung eine maximale relative Standardabweichung von 50 % aufweist.
- 10 30. Verfahren nach Anspruch 1, in dem die organische Lösung während der Zugabe der Fällungsflüssigkeit gerührt wird.

Revendications

- 15 1. Procédé pour produire des particules de dimensions uniformes d'un composé organique solide insoluble dans l'eau, qui comprend :
 - 20 (a) la préparation d'une solution du composé organique solide dans un solvant organique nuisible à l'eau pour le composé, ce composé organique solide ayant une solubilité aqueuse essentiellement petite;
 - (b) l'admission en filet d'un liquide précipitant aqueux dans la solution organique à une température entre -10°C et 100°C et à une vitesse d'admission en filet de 0,01 ml par minute à 1000 ml par minute par volume unitaire de 50 ml de la solution, de façon à produire une suspension du composé organique solide précipité sous la forme de particules sensiblement non agrégées d'une dimension uniforme choisie dans un intervalle de granulométrie moyenne s'élevant jusqu'à 10 microns (μm), où la granulométrie est ajustée par contrôle de la température de la solution et de la vitesse d'admission en filet, la granulométrie étant en relation directe avec la température de la solution pendant la précipitation et en relation inverse avec la vitesse d'admission en filet;
 - 25 (c) la séparation des particules des liquides organiques et leur lavage dans un liquide de lavage aqueux.
- 30 2. Procédé suivant la revendication 1, dans lequel un supplément de liquide précipitant aqueux est ajouté à la suspension avant que les particules soient séparées.
- 35 3. Procédé suivant la revendication 1, dans lequel les particules sont séparées par centrifugation, filtration sur membrane ou osmose inverse.
4. Procédé suivant la revendication 1, dans lequel le liquide de lavage aqueux est le même que le liquide précipitant aqueux.
- 40 5. Procédé suivant la revendication 1, dans lequel le liquide de lavage aqueux est pharmaceutiquement acceptable pour l'injection à un patient.
6. Procédé suivant la revendication 1, dans lequel le liquide précipitant aqueux est choisi dans la classe formée par l'eau et une solution aqueuse d'un sel minéral.
- 45 7. Procédé suivant la revendication 1, dans lequel le liquide précipitant aqueux est une solution de tensioactif.
8. Procédé suivant la revendication 1, dans lequel le liquide précipitant est une solution de tensioactif choisie dans la classe formée par 5% de polyvinylpyrrolidone dans de l'eau, 0,1% de polyvinylpyrrolidone dans de l'eau, 0,1% d'albumine de sérum humain dans de l'eau, 0,1% de Pluronic F-68 dans de l'eau, 0,33% de gélatine dans de l'eau, 0,33% de gélatine et 0,6% d'hydroxyéthylamidon dans de l'eau, 0,33% de gélatine et 0,02% de propylèneglycol dans de l'eau et 0,33% de gélatine et 2% de saccharose dans de l'eau.
- 50 9. Procédé suivant la revendication 1, dans lequel le liquide précipitant aqueux est admis en filet au moyen d'une aiguille d'un numéro courant.
- 55 10. Procédé suivant la revendication 1, dans lequel la granulométrie moyenne des particules est choisie dans l'intervalle de 0,01 micron à 0,1 micron (μm).

11. Procédé suivant la revendication 1, dans lequel la granulométrie moyenne des particules est choisie dans l'intervalle de 1 micron à 4 microns (μm).
- 5 12. Procédé suivant la revendication 1, dans lequel la granulométrie moyenne des particules est de 1 à 10 microns (μm).
13. Procédé suivant la revendication 1, dans lequel le composé organique solide a une solubilité aqueuse inférieure à une partie pour dix mille à la température ambiante.
- 10 14. Procédé suivant la revendication 1, dans lequel le composé organique solide est un composé organométallique.
- 15 15. Procédé suivant la revendication 1, dans lequel le composé organique solide est choisi dans la classe formée par un antinéoplasique, un antimicrobien, un antiviral, un anticoagulant, un antihypertenseur, un antihistaminique, un antipaludéen, un contraceptif, un antiépileptique, un dépresseur, un antidépresseur, un stéroïde adrénocortical, une hormone, un antagoniste d'hormone, un glycoside cardiaque, un immunosuppresseur, un bêta-bloquant, une vitamine insoluble dans l'eau, un sympathomimétique, un hypoglycémiant, un hyperglycémiant, un analgésique, un tranquillisant et un psychotrope.
- 20 16. Procédé suivant la revendication 1, dans lequel le composé organique solide est un ester éthylique d'un dérivé d'acide triodobenzoïque.
- 25 17. Procédé suivant la revendication 1, dans lequel le composé organique solide est choisi dans la classe formée par l'ester éthylique d'iodipamide, l'ester éthylique d'iothalamate, l'ester éthylique d'ioséfamate, la 2,2',4,4'-tétrahydroxybenzophénone, la RS-nitrocellulose, la progestérone, l'ester éthylique d'acide bêta-2,4,6-triiodo-3-diméthylformamidinophényl-propionique, l'isopropylpyrrolizine (NSC-278214), le 14-valérate de N-(trifluoroacétyl)-adriamycine et le 1,2-diaminocyclohexane malinate platine (II).
- 30 18. Procédé suivant la revendication 1, dans lequel le composé organique solide est choisi dans la classe formée par la noréthistérone, l'acide acétyl-salicylique, le wafarin, le complexe héparine-chlorure de tri-dodécylméthyl-ammonium, le sulfaméthoxazole, la céphalexine, l'acétate de prednisolone, le diazépam, le clonazépam, la méthidone, la naloxone, le disulfirame, la mercaptopurine, la digitoxine, la primaquine, la méfloquine, l'atropine, la scopolamine, le thiazide, le furosémide, le propranolol, le méthacrylate de méthyle, le poly(méthacrylate de méthyle), la 5-fluorodésoxyuridine, le cytosine arabinoside, l'acyclovir, le lévonorgestrel.
- 35 19. Procédé suivant la revendication 1, dans lequel le solvant organique est choisi dans la classe formée par le diméthylsulfoxyde, le diméthylformamide, le N,N'-diméthylacétamide, le phénol et l'isopropanol.
- 40 20. Procédé suivant la revendication 1, dans lequel le composé organique solide est un complexe de l'héparine, le solvant organique est l'isopropanol et le liquide précipitant aqueux est l'eau ou une solution aqueuse d'un sel minéral.
- 45 21. Procédé suivant la revendication 1, qui comprend de surcroît le stade de dilution de la solution organique avec un liquide non-solvant de façon que le rapport du non-solvant au solvant se situe entre 100:1 et 1:100 après la préparation de la solution et avant le stade d'admission en filet, la granulométrie étant en relation directe avec le rapport du non-solvant au solvant.
- 50 22. Procédé suivant la revendication 21, dans lequel le liquide non-solvant est un liquide dans lequel le composé organique solide est un peu plus soluble que dans l'eau.
23. Procédé suivant la revendication 21, dans lequel le liquide non-solvant est un alcool aliphatique inférieur.
24. Procédé suivant la revendication 21, dans lequel le composé organique solide est choisi dans la classe formée par l'ester éthylique d'iodipamide et l'ester éthylique d'ioséfamate, le solvant organique est le diméthylsulfoxyde, le liquide non-solvant est l'éthanol, le rapport de l'éthanol à la solution-organique est supérieur à 2,0 et la granulométrie moyenne des particules est supérieure à 1 micron (μm) en diamètre.
- 55 25. Procédé suivant la revendication 21, dans lequel le composé organique solide est choisi dans la classe formée par l'ester éthylique d'iodipamide et l'ester éthylique d'ioséfamate, le solvant organique est le di-

méthylsulfoxyde, le liquide non-solvant est l'éthanol, le rapport de l'éthanol à la solution organique est inférieur à 2,0 et la granulométrie moyenne des particules est inférieure à 1 micron (μm).

- 5 26. Procédé suivant la revendication 21, dans lequel le composé organique solide est l'ester éthylique d'iodipamide, le solvant organique est le diméthylsulfoxyde, le liquide non-solvant est l'éthanol, le liquide précipitant aqueux est la polyvinylpyrrolidone à 5% dans de l'eau, la température est de 4°C, la vitesse d'admission en filet (ml/minute) est égale à $23 + 0,14$ [vitesse d'agitation (tours par minute)] x [volume de solvant organique (litres)] et la granulométrie moyenne des particules est d'environ 1 micron (μm) en diamètre.
- 10 27. Procédé suivant la revendication 1, dans lequel la granulométrie moyenne des particules est choisie dans l'intervalle de 0,01 micron à 10 microns (μm).
- 15 28. Procédé suivant la revendication 1, dans lequel la granulométrie moyenne des particules est choisie dans l'intervalle de 0,01 micron à 5 microns (μm).
29. Procédé suivant la revendication 1, dans lequel le spectre granulométrique a un écart-type relatif maximum de 50%.
- 20 30. Procédé suivant la revendication 1, dans lequel la solution organique est agitée tandis que le liquide précipitant est admis en filet.

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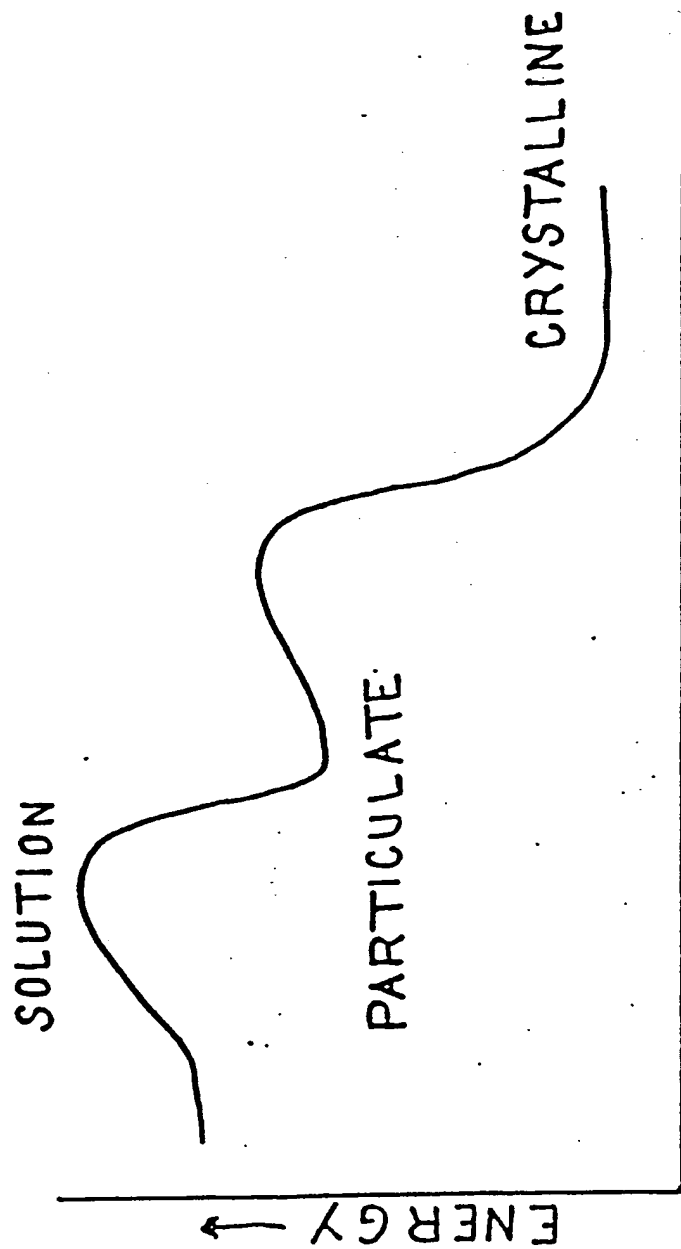


FIGURE 1

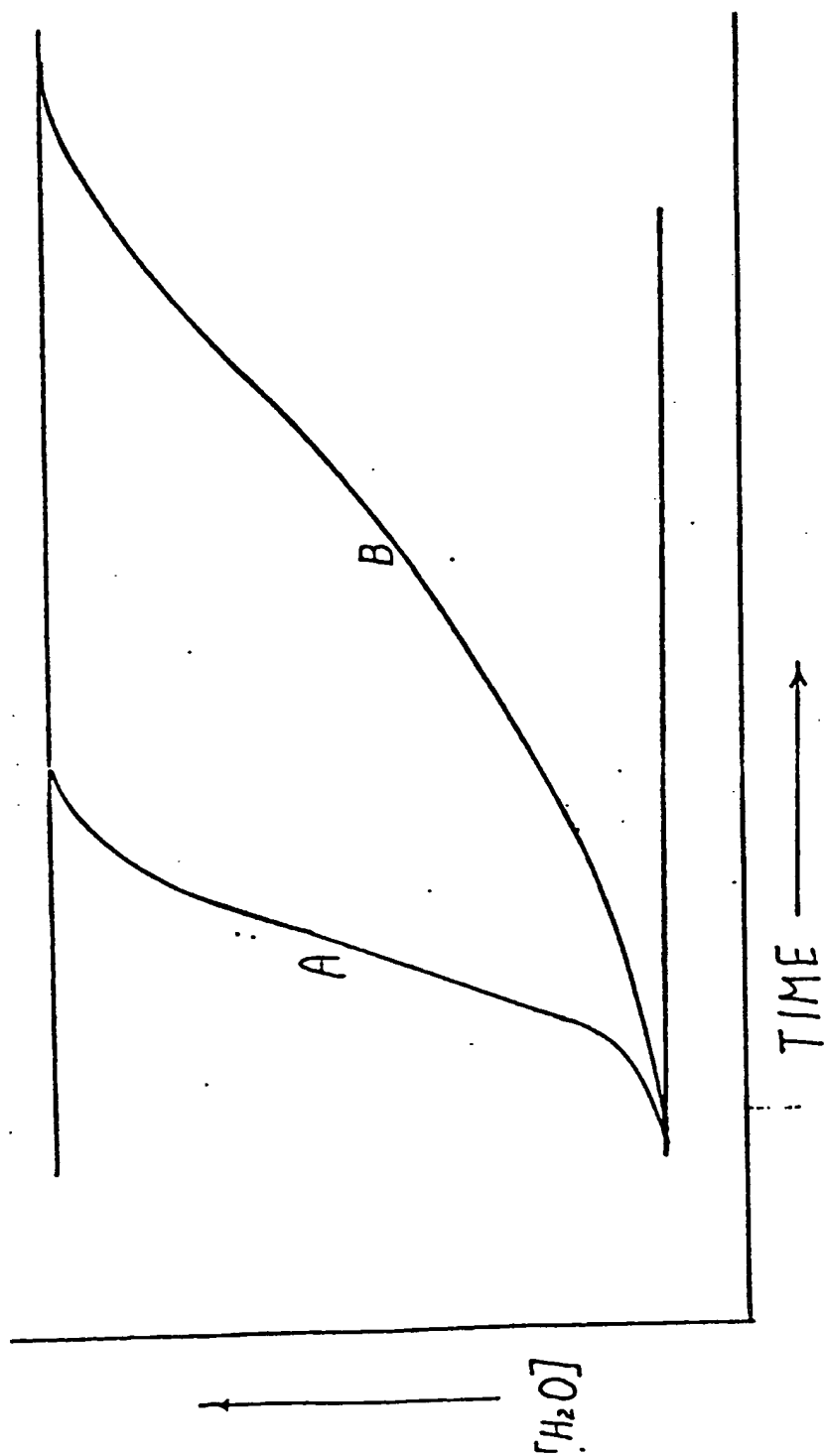


FIGURE 2

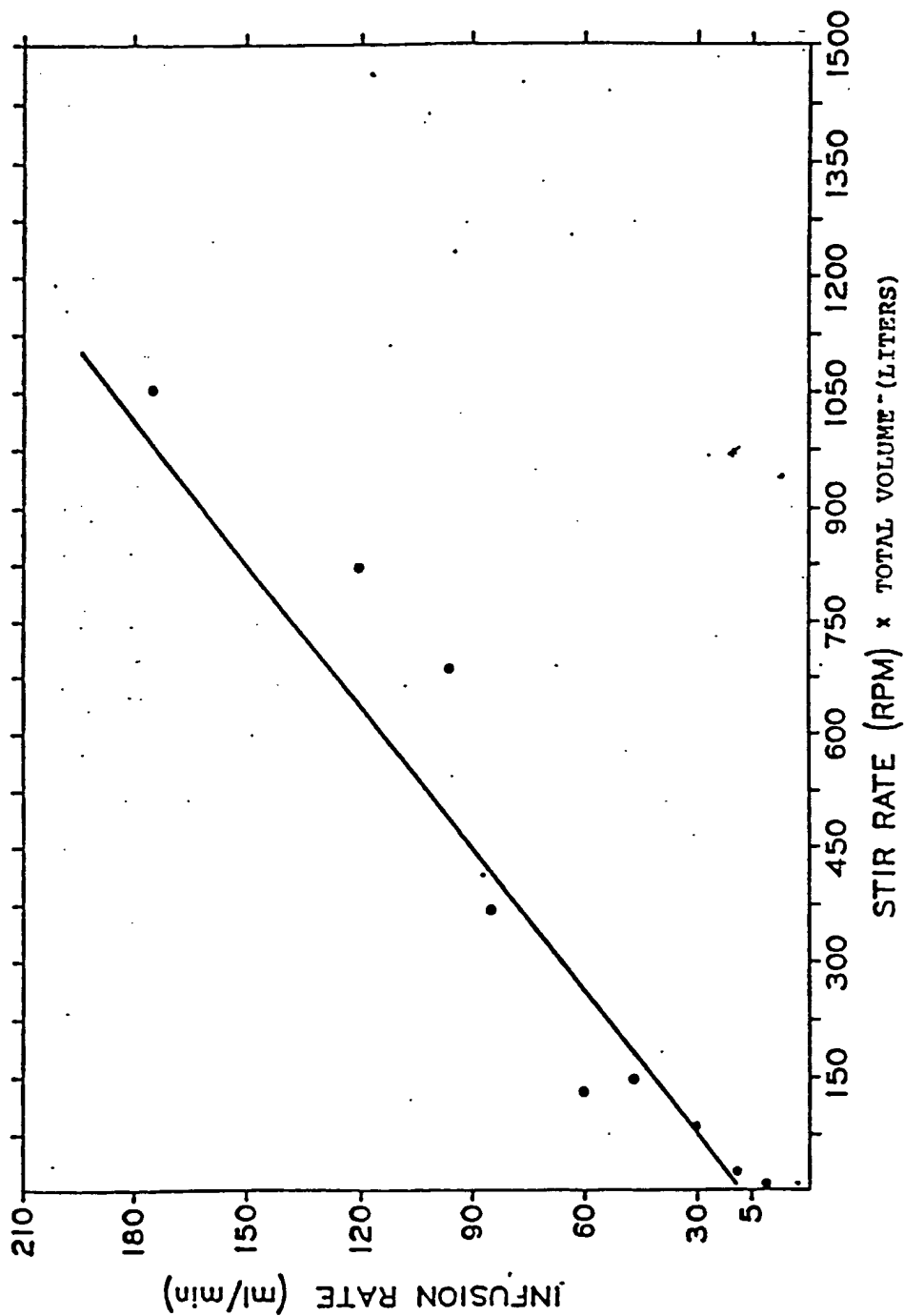


FIG. 3

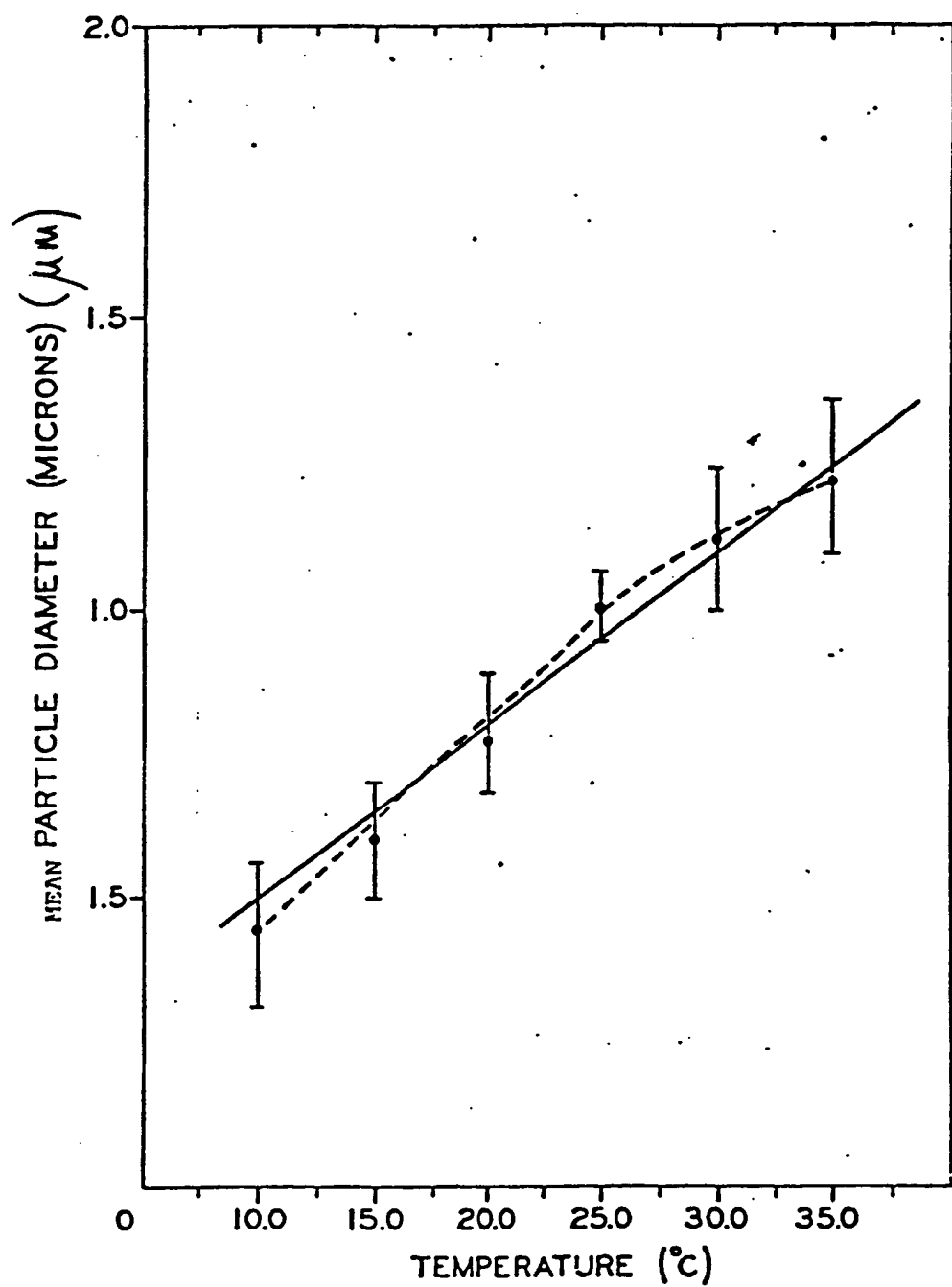
PARTICLE SIZE AS A
FUNCTION OF TEMPERATURE

FIG. 4

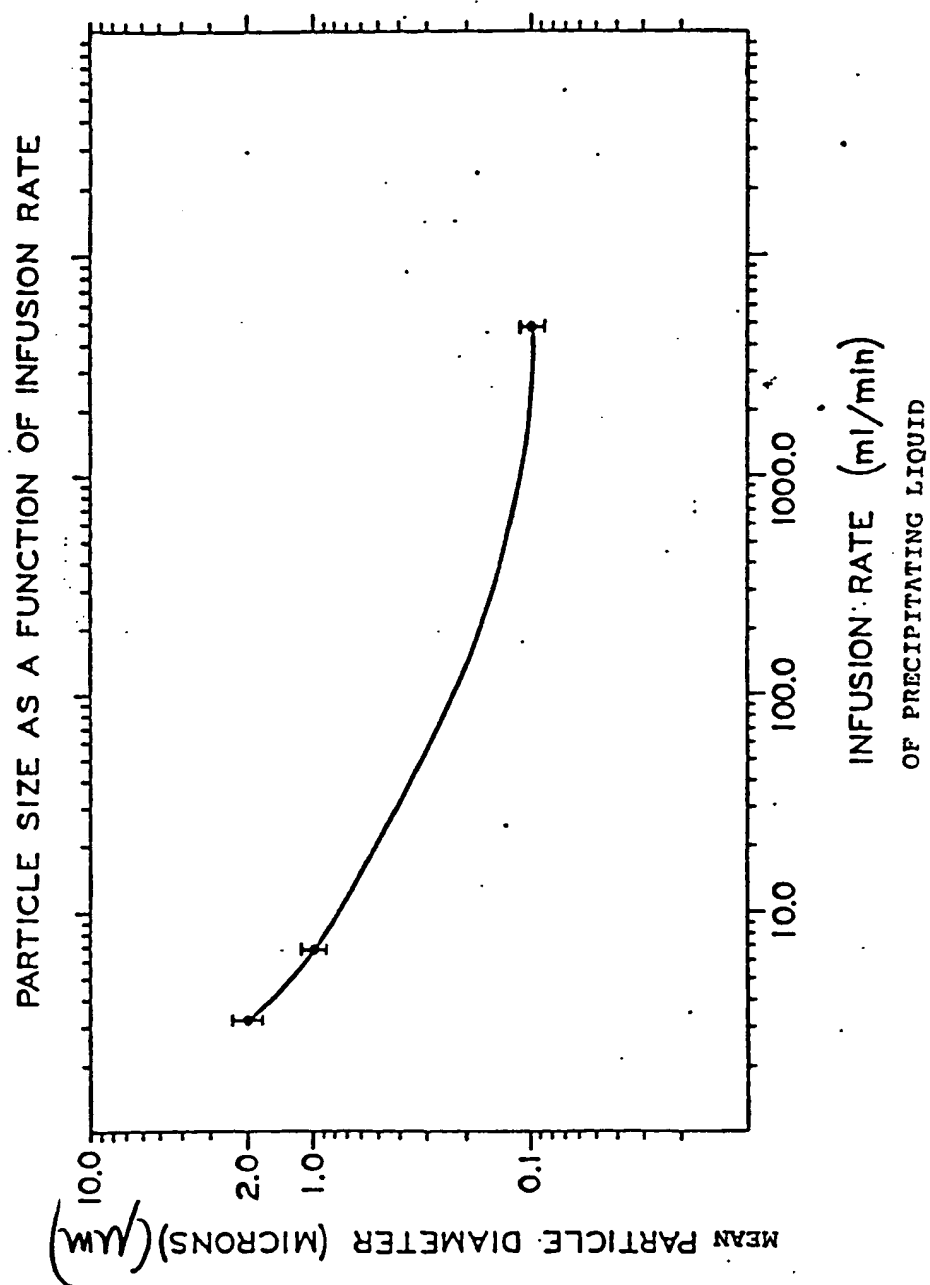


FIG. 5

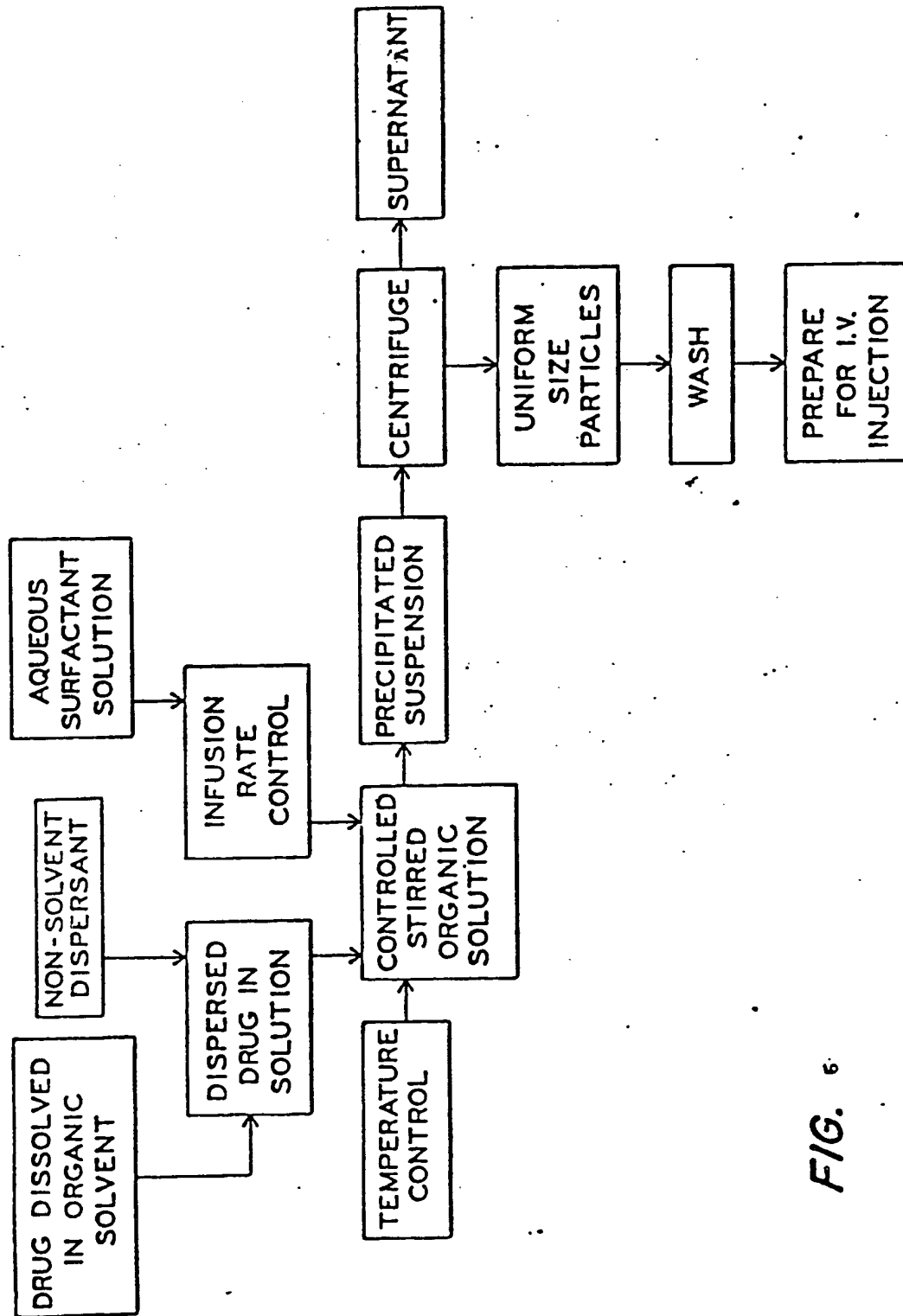


FIG. 6

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